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*The Annual Meeting of the Nutrition Society and the British Association for Parenteral and Enteral Nutrition was held at
The International Centre, Telford on 16–17 November 2005*

BAPEN Symposium 4 on ‘Glutamine and antioxidants in critical care’

Glutamine in critical care: current evidence from systematic reviews

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Glutamine, the most abundant amino acid in the body, is thought to become conditionally essential in critical illness. Some of the important roles for glutamine are as a carrier for inter-organ N, a preferred fuel for enterocytes and cells of the immune system, a substrate for renal NH₃ formation and a precursor for glutathione. Mechanisms by which glutamine could improve recovery include attenuating oxidant damage and inflammatory cytokine production, reducing gut bacterial translocation and improving N balance. The present systematic review has found trends to suggest that parenteral and enteral glutamine supplementation reduce mortality, the development of infection and organ failure in critical illness. Trials of parenteral nutrition containing glutamine with patients after elective surgery also suggest reduction of infection, but it is unlikely that glutamine-containing parenteral nutrition would be used for such patients. The evidence base is limited by the quality of the reported trials and the suggestion that there is publication bias, with trials suggesting reduced infection being more likely to be published.

Glutamine: Randomised controlled trials: Systematic reviews: Meta-analyses: Critical illness

The amino acid glutamine is the most abundant amino acid in the body. Plasma levels fall in critical illness, suggesting that glutamine could become limiting (Melis *et al.* 2004). Parenteral glutamine supplementation improves N balance (Stehle *et al.* 1989). Particular roles for glutamine include inter-organ N transport, a N donor for nucleotides and amino sugars and the key substrate for renal NH₃ formation. As a preferred fuel for enterocytes, glutamine may reduce bacterial translocation across the gut wall and thus the risk of sepsis (Melis *et al.* 2004; De-Souza & Greene, 2005). Cells of the immune system also utilise glutamine as fuel, and glutamine contributes to antioxidant defences (Eaton, 2006), e.g. through the production of glutathione (Melis *et al.* 2004). Glutamine enhances the expression of heat-shock protein, which is very important for protection against tissue damage in stress or injury (Singleton *et al.* 2005).

Until recently it has not been possible to include glutamine in parenteral nutrition for reasons of stability, but it is now possible. A systematic review of glutamine supplementation in serious illness (critically-ill patients or patients after surgery) published in 2002 (Novak *et al.* 2002) has found that glutamine supplementation in patients

after surgery may be associated with a reduction in infectious complications and shorter hospital stay. In critical illness glutamine appears to be associated with a reduction in complications and mortality. The greatest benefit appears to relate to the use of high-dose parenteral glutamine. The results of the meta-analyses are limited by the poor quality of many of the reported studies.

More recently, the Canadian clinical practice guidelines (Critical Care Connections Inc., 2005) for nutrition support in mechanically-ventilated critically-ill adult patients have recommended that where parenteral nutrition is prescribed it should be supplemented with glutamine, and that enteral glutamine should be considered for patients with burns and trauma. However, glutamine-containing parenteral or enteral nutrition has not been widely adopted in the UK for critical illness or after surgery. There have been few good-quality randomised controlled trials with adequate statistical power to evaluate glutamine use in these patient groups.

The response of patients after elective surgery and critically-ill patients to glutamine may differ (Heyland & Dhaliwal, 2005). In critical illness there is dramatic over-amplification of the inflammatory response, probably

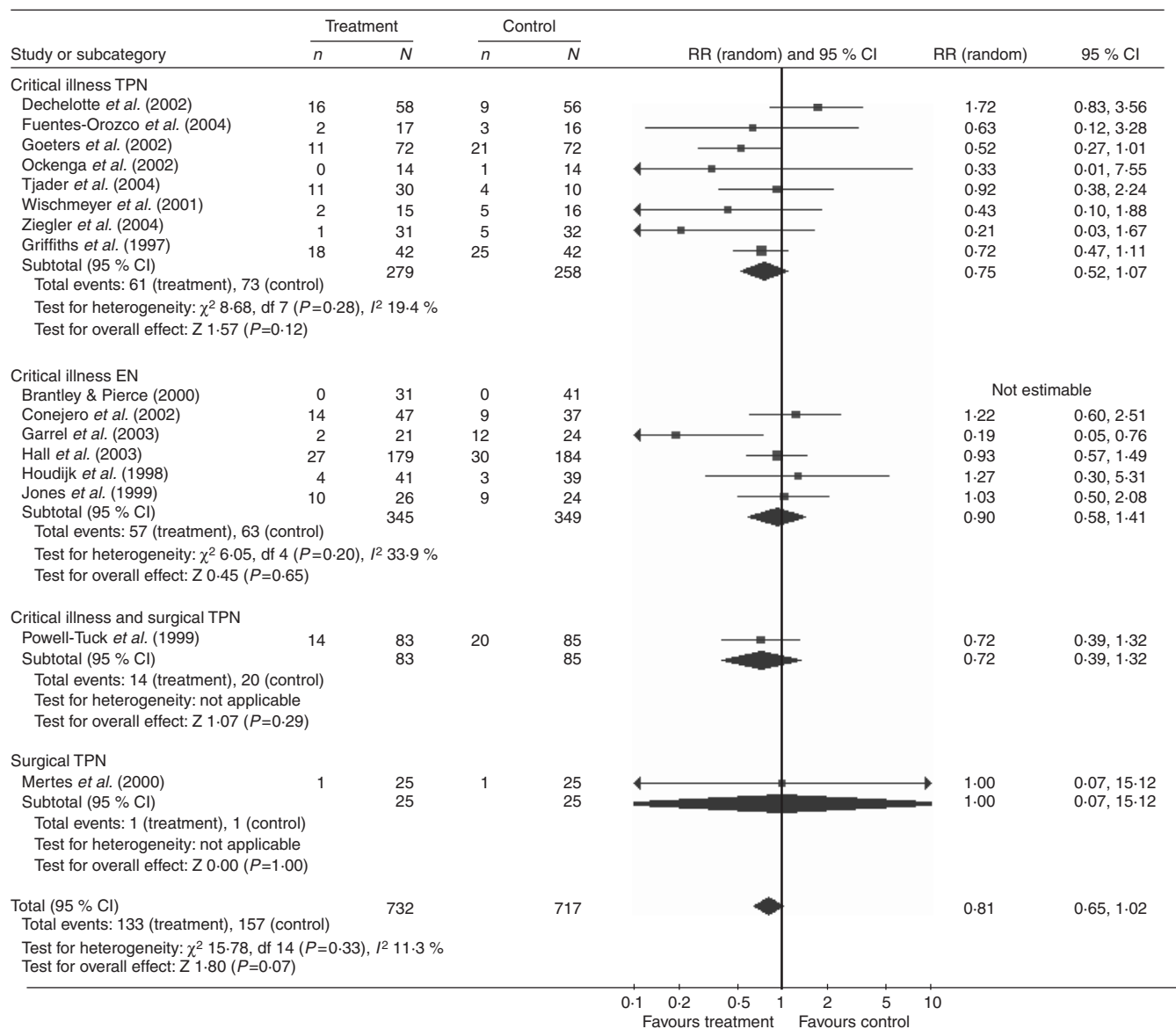


Fig. 1. A meta-analysis of glutamine-supplemented total parenteral nutrition (TPN) or enteral nutrition (EN) in critical illness and surgery to show the relative risks (RR) for mortality. *n*, No. of patients affected in the treatment group or control group; *N*, total no. of patients in the treatment group or control group. For details of analysis procedures, see p. 237 of proofs. \leftarrow , \rightarrow , Values extend beyond the range of values shown.

together with cellular immune dysfunction, whereas after surgery patients experience much less cytokine activation and some suppression of cell-mediated immunity, which increases the risk of infection. The present systematic review considers separately critically-ill patients and patients who have undergone surgery, as well as combining the evidence from randomised controlled trials for these patient groups.

Methods

A systematic review and meta-analyses were undertaken of randomised controlled trials comparing glutamine-containing parenteral or enteral nutrition with control feeding. It was assumed that regimens given to intervention and control groups were approximately isonitrogenous

and isoenergetic, but the amounts administered and whether this assumption was valid was not always clear in the reports. Trials evaluating immunonutrition feeding regimens in which glutamine was one of several other nutrients, e.g. arginine or *n*-3 fatty acids, were not included. Patient groups were adults with critical illness or post surgery.

Trials were identified by searching five electronic databases (Medline, Embase, CABNAR, Cinahl, Healthstar), hand searching four journals (*Clinical Nutrition*, *Journal of Parenteral and Enteral Nutrition*, *Intensive Care Medicine*, *Critical Care Medicine*) and from previous reviews, including that by Novak *et al.* (2002). Full published reports, conference proceedings and abstracts provided data. The last date for the search was August 2005.

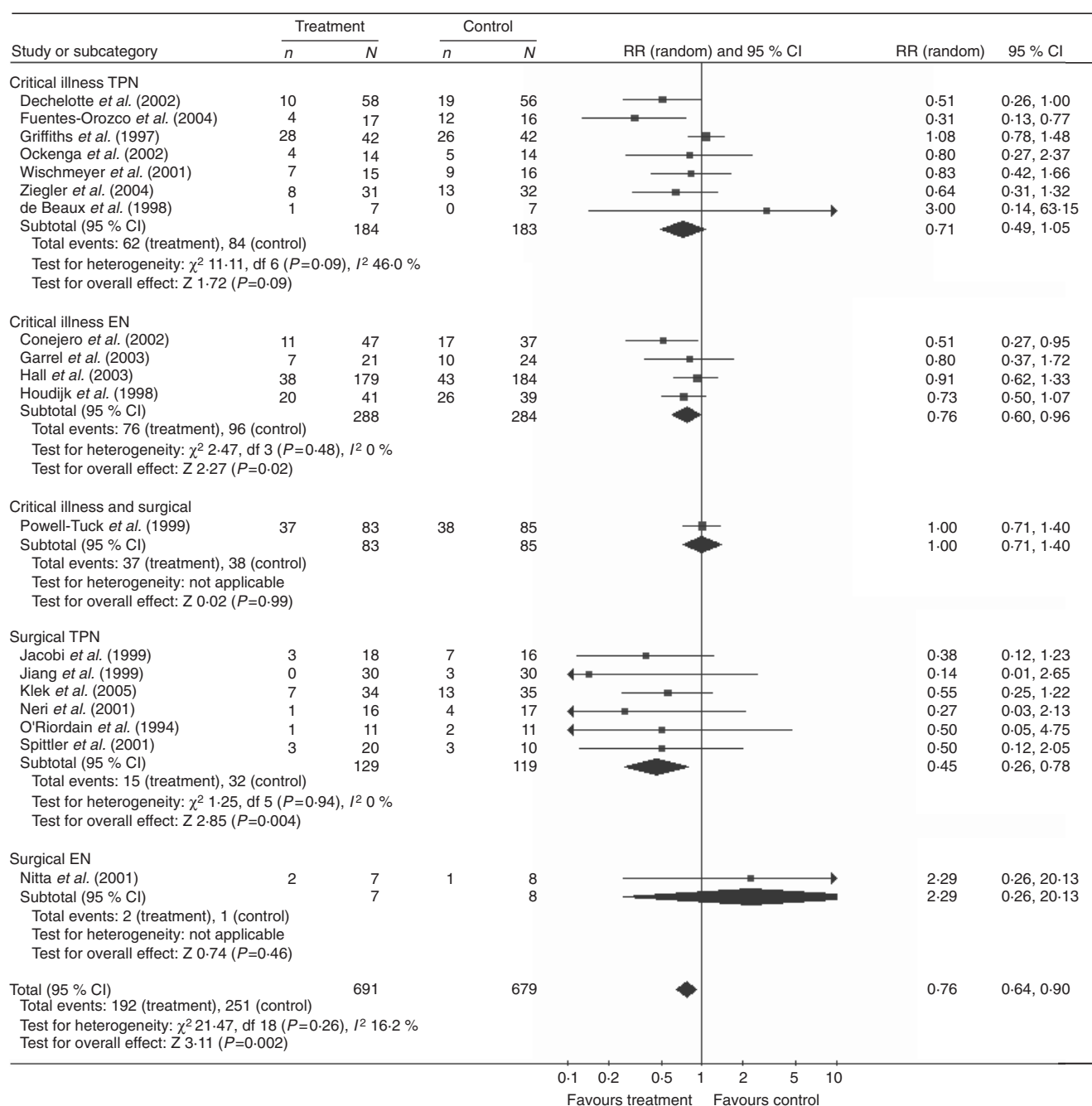


Fig. 2. A meta-analysis of glutamine-supplemented total parenteral (TPN) or enteral (EN) nutrition in critical illness and surgery to show the relative risks (RR) for participants with infection. *n*, No. of patients affected in the treatment group or control group; *N*, total no. of patients in the treatment group or control group. For details of analysis procedures, see p. 237 of proofs. \leftarrow , \rightarrow , Value extends beyond the range of values shown.

Data on deaths, participants with infection and participants with organ failure are presented. A conservative method of data handling was used. Outcomes were taken from the last available time of follow-up, with a random-effects model for meta-analysis. Data are presented with all participants randomised as the denominator. Heterogeneity amongst trials was assessed by the I^2 statistic (Higgins *et al.* 2003), where $\geq 50\%$ was taken as indicating significant heterogeneity. Publication bias was examined by

funnel-plot analysis (Sterne *et al.* 2001). Analyses were undertaken using Review Manager version 4.2.7 software (The Cochrane Collaboration, Oxford, UK). Relative risks (RR) and 95% CI are reported.

Results

Fifteen trials were identified for patients with critical illness (including seven trials with a mixed intensive care

unit population, two trials with patients with trauma, four trials with patients with pancreatitis or surgical complications). There were eleven trials with patients who had undergone elective surgery (nine trials with patients undergoing gastrointestinal surgery (only one of which indicated that patients required parenteral nutrition), one trial with patients undergoing cystectomy, one trial with patients having abdominal aortic aneurysm repair). One further trial, undertaken in a UK hospital, evaluated glutamine-containing parenteral nutrition with a mixed hospital population cared for by the nutrition team (Powell-Tuck *et al.* 1999). However, not all trials provided data that could be incorporated into the meta-analyses.

Trial quality, as reported, was often limited, particularly in terms of reporting concealment of randomisation, intention-to-treat analysis and blinding of outcome assessment (although this issue is not likely to be a problem for reporting of deaths).

Mortality

Parenteral glutamine in critical illness was associated with a non-significant reduction in mortality (RR 0.75 (95% CI 0.52, 1.07); Fig. 1). For enteral glutamine in critical illness the RR was 0.90 (95% CI 0.58, 1.41). Only one surgical trial reported mortality and one trial reported for a mixed hospital population, in neither case was there a significant reduction. Overall, for all population groups combined the RR for mortality was 0.81 (95% CI 0.65, 1.02). Thus, there is a strong trend for a beneficial effect, most clearly for parenteral glutamine in critical illness.

Participants with infection

For enteral glutamine in critical illness (often patients with trauma or burns) there was a significant reduction in infection among participants (RR 0.76 (95% CI 0.60, 0.96); Fig. 2). For parenteral glutamine in critical illness there was a trend for a reduction in infections (RR 0.71 (95% CI 0.49, 1.05)). In patients who had undergone surgery and were given parenteral nutrition containing glutamine, whether they required parenteral nutrition or not, there was a significant reduction in infection among participants (RR 0.45 (95% CI 0.26, 0.78)). Overall, for all patient groups there was a significant reduction in infection among participants (RR 0.76 (95% CI 0.64, 0.90)).

For the outcome of participants with infection, which provides the most data, a funnel plot examining for the suggestion of publication bias was undertaken (Fig. 3). The individual data points should be evenly distributed in an inverted 'V' on either side of the vertical axis. The plot clearly shows fewer data points to the right of the line, suggesting that small trials with positive results are more likely to be published. The suggestion of publication bias can be tested (Sterne *et al.* 2001); this test also suggests publication bias ($P = 0.03$).

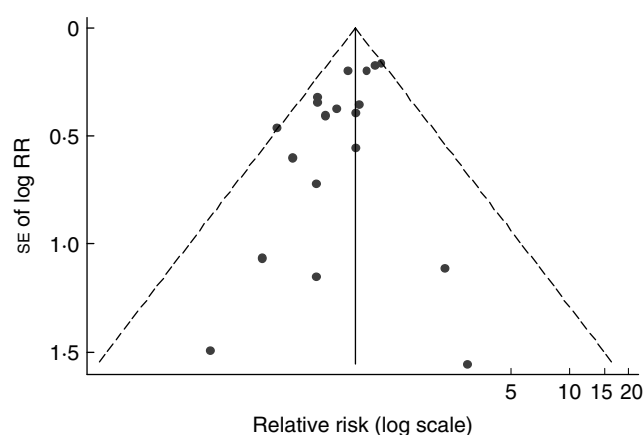


Fig. 3. Funnel-plot examination for publication bias for data from the meta-analysis of glutamine-supplemented parenteral nutrition (PN) or enteral nutrition (EN) in critical illness and surgery for the relative risks for participants with infection (data shown in Fig. 2; $P = 0.03$, suggesting publication bias).

Participants with multi-organ or renal failure

Few trials have reported multi-organ or renal failure. Combining all parenteral glutamine trials (Fig. 4) there was a significant reduction (RR 0.67 (95% CI 0.46, 0.98)), but not for enteral glutamine (RR 1.15 (95% CI 0.70, 1.87)). Overall, there was no suggestion that glutamine was harmful in terms of multi-organ or renal failure (RR 0.82 (95% CI 0.61, 1.10)).

Conclusions

Overall, there is no suggestion that parenteral or enteral glutamine is harmful, and trends in the data suggest beneficial effects. However, the results have to be interpreted with caution in view of the poor quality of the trials and the suggestion from the funnel plot that trials with positive results are more likely to be published. In addition, not all trials reported all outcomes, so that even published trialists may be selectively reporting outcomes.

The categorisation into critical illness or surgical trials was not always straightforward. In the present analysis trials in which the participants had pancreatitis or had undergone surgery, followed by complications (e.g. peritonitis), were classified as critical illness. However, it is clear that almost all the surgical trials of parenteral glutamine gave parenteral nutrition to patients after uncomplicated elective surgery, when parenteral nutrition would not have been provided in clinical practice. Given that parenteral nutrition itself may be associated with an increased risk of infection (Simpson & Doig, 2005), it is unclear how the reduction in infection with parenteral glutamine for this group of post-surgery patients can be interpreted.

There is clearly a need to evaluate the use of glutamine further in adequately-powered randomised controlled trials in critical illness and patients with surgical complications. Trials in the UK, Canada and Sweden are being initiated to examine the effect of parenteral glutamine, in parenteral nutrition and supplementary to nutrition support.

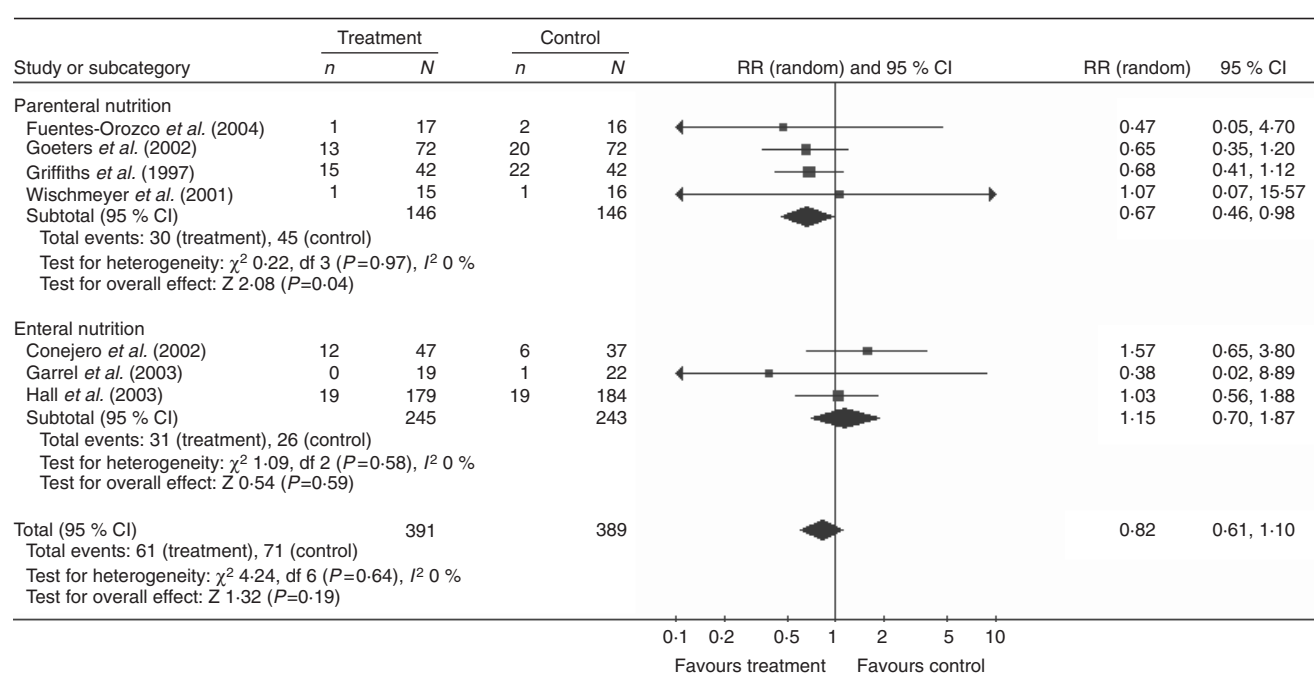


Fig. 4. Meta-analysis of glutamine-supplemented parenteral or enteral nutrition in critical illness and surgery to show the relative risks (RR) for participants developing multiorgan or renal failure. *n*, No. of patients affected in the treatment group or control group; *N*, total no. of patients in the treatment group or control group. For details of analysis procedures, see p. 237 of proofs. ←, →, Value extends beyond the range of values shown.

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The Medical Research Council, Chief Scientist Office, Fresenius-Kabi and Oxford Nutrition have provided funds for the SIGNET trial of glutamine and/or selenium-supplemented parenteral nutrition in intensive care. Daren Heyland and his group (Canadian Critical Care Trials Group) initiated the systematic review in this area. Anne Milne and Bernie Croal helped with data extraction on more recent trials.

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